Gemeinsamer Bundesausschuss

Resolution

of the Federal Joint Committee on an Amendment of the Pharmaceuticals Directive (AM-RL):

Annex XII - Benefit Assessment of Medicinal Products with New Active Ingredients according to Section 35a SGB V: Olaparib (new therapeutic indication: adenocarcinoma of the pancreas, BRCA1/2-mutations, maintenance treatment)

of 3 June 2021

At its session on 3 June 2021, the Federal Joint Committee (G-BA) resolved to amend the Pharmaceuticals Directive (AM-RL) in the version dated 18 December 2008/22 January 2009 (Federal Gazette, BAnz. No. 49a of 31 March 2009), as last amended on DD. Month YYYY (Federal Gazette, BAnz AT DD.MM.YYYY BX), as follows:

I. **In Annex XII, the following information shall be added after No. 4 to the information on the benefit assessment of olaparib in accordance with the resolution of 16 January 2020:**

Olaparib

Resolution of: 3 June 2021
Entry into force on: 3 June 2021
BAnz AT TT. MM YYYY Bx

New therapeutic indication (according to the marketing authorisation of 3 July 2020):

Lynparza is indicated as monotherapy for the maintenance treatment of adult patients with germline BRCA1/2-mutations who have metastatic adenocarcinoma of the pancreas and have not progressed after a minimum of 16 weeks of platinum treatment within a first-line chemotherapy regimen.

Therapeutic indication of the resolution (resolution of 3 June 2021):

"see new therapeutic indication according to marketing authorisation"

1. Additional benefit of the medicinal product in relation to the appropriate comparator therapy

Adult patients with germline BRCA1/2-mutations who have metastatic adenocarcinoma of the pancreas and have not progressed after minimum of 16 weeks of platinum treatment within a first-line chemotherapy regimen as maintenance treatment

Appropriate comparator therapy:

Monitoring wait-and-see approach

Extent and probability of the additional benefit of Olaparib compared to a monitoring wait-and-see approach:

An additional benefit is not proven.

Study results according to endpoints:[1]

[1] Data from the dossier assessment of the Institute for Quality and Efficiency in Health Care (IQWiG) (A120-115) unless otherwise indicated.

Summary of results of relevant clinical endpoints

Endpoint category	Effect direction/ Risk of bias	Summary
Mortality	↔	No relevant difference for the benefit assessment.
Morbidity	↓	Disadvantages in the endpoint Nausea and vomiting
Health-related quality of life	↔	No relevant difference for the benefit assessment.
Side effects	↔	No relevant difference for the benefit assessment.

Explanations:
↑: statistically significant and relevant positive effect with low/unclear reliability of data
↓: statistically significant and relevant negative effect with low/unclear reliability of data
↑↑: statistically significant and relevant positive effect with high reliability of data
↓↓: statistically significant and relevant negative effect with high reliability of data
↔: no statistically significant or relevant difference
∅: There are no usable data for the benefit assessment.
n.a.: not assessable

POLO study: randomised, double-blind, multi-centre study comparing olaparib with placebo. Results from data cut-off on 15.1.2019 (DCO1).

Mortality

Endpoint	Olaparib		Placebo		Olaparib vs placebo
	N	Median time to event in months [95% CI] Patients with event n (%)	N	Median time to event in months [95% CI] Patients with event n (%)	HR [95% CI]; p-value[a] Absolute difference (AD)[b]
Overall survival					
	92	18.9 [14.9; 26.2] 41 (44.6)	62	18,1 [12,6; 26,1] 30 (48,4)	0.91 [0.56; 1.46] 0.683

Morbidity

Progression-free survival (PFS)[f]					
	92	7.4 [4.1; 11.0] 60[c] (65.2)	62	3.8 [3.5; 4.9] 44[c] (71.0)	0.53 [0.35; 0.82]; 0.0038[d] AD= 3.6 months
Symptomatology					

EORTC QLQ-C30 (symptom scales, time to confirmed clinically relevant deterioration[e])					
Fatigue	89	12.0 [4.6; n. c.] 37 (41.6)	58	n. a. 17 (29.3)	1.36 [0.79; 2.36] 0.267
Nausea and vomiting	89	n. a. 35 (39.3)	58	n. a. 8 (13.8)	**2.60 [1.42; 4.77]** **0.002**
Pain	89	7,4 [3,7; 14,1] 42 (47,2)	58	4,6 [2,9; 6,0] 30 (51,7)	0.69 [0.42; 1.13] 0.144
Dyspnoea	89	n. a. 20 (22.5)	58	n. a. 7 (12.1)	1.54 [0.70; 3.39]; 0.284
Insomnia	89	n. a. 24 (27.0)	58	12.1 [5.7; n. c.] 16 (27.6)	0.73 [0.38; 1.42]; 0.351
Loss of Appetite	89	n. a. 28 (31.5)	58	n. a. 9 (15.5)	1.74 [0.89; 3.40]; 0.103
Constipation	89	n. a. 25 (28.1)	58	20,3 [12,5; n. c.] 8 (13.8)	1.77 [0.87; 3.59]; 0.112
Diarrhoea	89	30,4 [30,4; n. c.] 14 (15.7)	57	n. a. 6 (10.5)	1.10 [0.42; 2.90]; 0.840
EORTC QLQ-PAN26 (symptom scales, time to confirmed clinically relevant deterioration[e])					
Abdominal pain	88	13.0 [7.4; n. c.] 33 (37.5)	58	6.0 [4.6; n. c.] 23 (39.7)	0.70 [0.40; 1.23]; 0.214
Metabolism disorders	88	n. a. 27 (30.7)	58	n. a. 11 (19.0)	1.32 [0.68; 2.58]; 0.413
altered stool habits	88	n. a. 18 (20.5)	58	n. a. 7 (12.1)	1.43 [0.63; 3.26]; 0.391
hepatic symptomatology	88	22.1 [16.6; n. c.] 19 (21.6)	58	n. a. 10 (17.2)	0.82 [0.37; 1.84]; 0.628
Flatulence	88	15,7 [10,4; n. c.] 29 (33.0)	58	12,1 [5,6; n. c.] 18 (31.0)	0.91 [0.50; 1.66]; 0.760
Indigestion	88	n. a. 19 (21.6)	58	n. a. 10 (17.2)	1.03 [0.48; 2.21]; 0.946
Flatulence	88	n. a. 22 (25.0)	58	n. a. 10 (17.2)	1.29 [0.63; 2.66]; 0.483
Weight loss	88	n. a. 14 (15.9)	58	n. a. 3 (5.2)	2.11 [0.76; 5.85]; 0.153
Muscle weakness in arms and legs	88	n. a. 20 (22.7)	58	n. a. 7 (12.1)	1.59 [0.73; 3.50]; 0.245

Impairment due to side effects	87	n. a. 20 (23.0)		57	n. a. 8 (14.0)		1.47 [0.68; 3.17]; 0.325
Dry mouth	88	n. a. 13 (14.8)		58	n. a. 12 (20.7)		0.55 [0.24; 1.25]; 0.154
Dysgeusia	87	n. a. 8 (9.2)		58	n. a. 3 (5.2)		1.37 [0.39; 4.82]; 0.624
Endpoint	**Olaparib**			**Placebo**			**Olaparib vs placebo**
	N[h]	Values at start of study MV (SD)	Change up to cycle 6 MV (SE)[i]	N[h]	Values at start of study MV (SD)	Change up to cycle 6 MV (SE)[i]	MD [95% CI]; p-value [i, j]
health status							
EQ-5D VAS[k]	84	75.90 (15.89)	−0.65 (1.07)	53	77,50 (18.16)	−1.01 (1.47)	0.37 [−3.23; 3.96]; 0.840

Health-related quality of life

Endpoint	**Olaparib**		**Placebo**		**Olaparib vs placebo**
	N	Median time to event in months [95% CI] Patients with event n (%)	N	Median time to event in months [95% CI] Patients with event n (%)	HR [95% CI]; P value[a] Absolute difference (AD)[b]

EORTC QLQ-C30 (Functional scales; time to confirmed clinically relevant deterioration[g])					
global health status	89	34.3 [21.2; n. c.] 25 (28.1)	58	n. a. 19 (32.8)	0.66 [0.35; 1.24]; 0.199
Physical function	89	n. a. 22 (24.7)	58	n. a. 10 (17.2)	1.36 [0.66; 2.77]; 0.403
Role function	89	19,4 [13,8; n. c.] 32 (36.0)	58	n. a. 16 (27.6)	1.16 [0.64; 2.09]; 0.631
Cognitive function	89	n. a. 23 (25.8)	58	n. a. 14 (24.1)	0.97 [0.49; 1.89]; 0.921
Emotional function	89	16,6 [12,2; n. c.] 24 (27.0)	58	8,3 [5,7; n. c.] 18 (31.0)	0.66 [0.35; 1.26] 0.204
Social function	89	26,9 [11,9; n. c.] 26 (29.2)	58	n. a. 9 (15.5)	1,52 [0,75; 3,06] 0,241
EORTC QLQ-PAN26 (time to confirmed clinically relevant deterioration[g])					
Satisfaction with medical care[g]	88	n. a. 26 (29.5)	57	n. a. 10 (17.5)	1.43 [0.72; 2.84]; 0.303
Sexuality[g]	84	n. a. 17 (20.2)	56	n. a. 8 (14.3)	1.21 [0.53; 2.73]; 0.654
Body image[e]	88	n. a. 19 (21.6)	57	n. a. 9 (15.8)	1.17 [0.54; 2.55]; 0.687
Worried about the future[e]	87	n. a. 13 (14.9)	57	n. a. 5 (8.8)	1.42 [0.54; 3.76]; 0.477
Restrictions in the planning of activities[e]	88	26,9 [21,2; n. c.] 22 (25.0)	56	n. a. 6 (10.7)	1.78 [0.81; 3.93]; 0.153

Side effects

Endpoint	**Olaparib**		**Placebo**		**Olaparib vs placebo**
	N	Median time to event in months [95% CI] Patients with event n (%)	N	Median time to event in months [95% CI] Patients with event n (%)	HR [95% CI]; P value[a]
Adverse events (AE) in total					
	91	0.2 [0.1; 0.3] 87 (95.6)	60	0.3 [0.1; 0.3] 56 (93.3)	-

Serious adverse events (SAE)					
	91	38.7 [15.6; n. c.] 22 (24.2)	60	n. a. 9 (15.0)	1.24 [0.58; 2.65] 0.582
Severe adverse events (CTCAE grade 3 or 4)					
	91	11.9 [7.2; n. c.] 36 (39.6)	60	19.4 [12.9; n. c.] 14 (23.3)	1.38 [0.77; 2.48] 0.280
Therapy discontinuation due to adverse events					
	91	n. a. 5 (5.5)	60	n. a. 1 (1.7)	2.29 [0.41; 12.64]; 0.342
Specific adverse events					
Decreased appetite (PT, UE)	91	n. a. 23 (25.3)	60	n. a. 4 (6.7)	**2.93 [1.36; 6.32]; 0.006**
Urinary tract infection (PT, AE)	There are no evaluable data				
myelodysplastic syndrome e (PT, AE)	There are no evaluable data				
acute myeloid leukaemia e (PT, AE)	There are no evaluable data				

a: HR and CI: Log-rank test statistic; p-value: Log-rank test; each without stratification
b: Indication of absolute difference (AD) only in case of statistically significant difference; own calculation.
c: Number of patients with event. Patients who did not show progression and did not die or patients who did show progression after two or more missed visits were censored to the last RECIST assessment performed (version 1.1) or to Day 1 if there was no completed visit. Patients who have not performed visit or had no baseline data were censored at day 1 unless they died within two visits of baseline.
d: Analysis using an unstratified log-rank test and applying the Breslow approach.
e: Confirmed clinically relevant deterioration is defined as an increase of ≥ 10 points on 2 consecutive visits. Patients who died before a confirmed clinically relevant deterioration were censored.
f: Data from module 4 of the pU
g: Confirmed clinically relevant deterioration is defined as a decrease of ≥ 10 points on 2 consecutive visits. Patients who died before a confirmed clinically relevant deterioration were censored.
h: Number of patients included in the evaluation to calculate the effect estimate, the values at baseline are based on all patients for whom a measurement at baseline and at least one subsequent measurement were available.
i. MMRM model adjusted for treatment, visit and value at baseline, and interaction terms for treatment and visit, value at baseline and visit.
j: Effect represents the difference between treatment groups of changes from study entry to cycle 6.
k: Higher (increasing) values mean better health-related quality of life; positive effects (intervention minus control) mean an advantage for the intervention.

Abbreviations used:
AD = Absolute Difference; CTCAE = Common Terminology Criteria for Adverse Events; CTCAE: Common Terminology Criteria for Adverse Events; EORTC: European Organisation for Research and Treatment of Cancer; EQ-5D: European Quality of Life Questionnaire 5 Dimensions; HR = hazard ratio; CI = confidence interval; MD: Mean difference; MMRM: mixed model with repeated measures; MV: Mean value; N = number of patients evaluated; n= number of patients with (at least one) event; n.c. = not calculable; n.a. = not achieved; PT = preferred term; QLQ-C30: Quality of Life Questionnaire Core 30; QLQ-PAN26: Quality of Life Questionnaire and Pancreatic Cancer Module; SD: Standard deviation; SE: standard error; SMD: Standardised mean difference; VAS: visual analogue scale; vs = versus.

2. Number of patients or demarcation of patient groups eligible for treatment

Patient populations

approx. 75 to 95 patients

3. Requirements for a quality-assured application

The requirements in the product information are to be taken into account. The European Medicines Agency (EMA) provides the contents of the product information (summary of product characteristics, SmPC) for Lynparza (active ingredient: olaparib) at the following publicly accessible link (last access: 15 May 2021).
https://www.ema.europa.eu/documents/product-information/lynparza-epar-product-information_de.pdf

Treatment with olaparib should only be initiated and monitored by specialists in internal medicine, haematology, and oncology and specialists participating in the Oncology Agreement who are experienced in the treatment of patients with adenocarcinoma of the pancreas.

4. Treatment costs

Annual treatment costs:

Name of therapy	Annual treatment costs/patient
Medicinal product to be assessed:	
Olaparib	€ 69,059,30
Appropriate comparator therapy:	
Monitoring wait-and-see approach	incalculable

Cost after deduction of statutory rebates (LAUER-TAXE®, as last revised: 15 May 2021).

Costs for additionally required SHI services: not applicable

II. The resolution will enter into force on the day of its publication on the internet on the G-BA website on 3 June 2021.

The justification to this resolution will be published on the G-BA website at www.g-ba.de.

Berlin, 3 June 2021

Federal Joint Committee
in accordance with Section 91 SGB V
The chairman

Prof. Hecken